PROCESS FOR MAKING ORALLY CONSUMABLE DOSAGE FORMS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/403,887 filed August 16, 2002 and U.K. Application No. 0217382.1 filed 26 July 2002.

The present invention is concerned with a process for making rapidly dissolving and dispersing dosage forms, particularly orally consumable films, for the delivery of pharmaceutically active agents and with the dosage forms so obtained.

The use of orally consumable dosage forms, particularly films, to deliver pharmaceutically active agents is well known in the art.

Thus WO 98/20862 describes a preparation for application in the oral cavity with one layer or film which adheres to the mucous membrane, characterised in that the adhesive layer or film contains a homogenous mixture consisting of a water soluble polymer, a mixture of non-ionic surface active materials, a polyalcohol, a cosmetic or pharmaceutical active substance, and a food flavouring or aromatic agent.

WO 98/26780 describes a solid medicament preparation, which can decompose in aqueous media and has a flat-, foil-, paper- or wafer-type presentation for the application and release of active substances in the buccal cavity. The invention is characterised in that it contains buprenorphine, or an active substance, which is pharmacologically comparable thereto, or a therapeutically suitable salt of buprenorphine or of the pharmacologically comparable active substance.

WO 98/26763 describes a medicament preparation with a flat-, paper- or wafer-like presentation for the application and release of active substances into the buccal cavity. The preparation is characterised in that it contains apomorphine or one of its therapeutically suitable salts.

WO 99/17753 describes a rapidly soluble filmy preparation comprising a drug, an edible and readily soluble high-molecular substance and a sugar, which is rapidly soluble in the oral cavity.

WO 00/18365 describes physiologically acceptable films, including edible films, which include a water-soluble film-forming polymer such as pullulan. Edible films including pullulan and antimicrobially effective amounts of the essential oils thymol, methyl salicylate, eucalyptol and menthol are effective at killing the plaque-producing germs that cause dental plaque, gingivitis and bad breath. The film can also contain pharmaceutically active agents.

WO 01/70194 describes physiologically acceptable films, including edible films, which include a water-soluble film-forming polymer, such as pullulan, and a taste-masked pharmaceutically active agent, such as dextromethorphan. The taste-masking agent is preferably a sulphonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene, such as Amberlite™.

WO 01/70194 describes a method for preparing the orally consumable film of the invention, which comprises

(a) dissolving water-soluble ingredients in water to provide an aqueous solution;

(b) mixing at least one water-soluble film former and at least one stabilising agent to provide a film-forming mixture;

(c) combining the film-forming mixture and the aqueous solution to provide a hydrated polymer gel;

(d) mixing oils to form an oil mixture;

(e) adding the oil mixture to the hydrated polymer gel and mixing to provide a uniform gel;

(f) casting the uniform gel on a substrate; and

(g) drying the cast to provide a film.

The difficulty associated with a process of this type is that a high viscosity composition, typically a gel, is required in order to achieve a satisfactory cast. It follows that the resulting dosage form gives rise to a viscous solution when placed in the mouth of the consumer. This may be satisfactory for the delivery of oral healthcare products, such as mouthwashes, which are intended to remain in the mouth for some time, but such dosage forms do not lend themselves to the delivery of pharmaceutically active agents, which need to be rapidly dissolved and dispersed as soon as the dosage form is placed in the mouth. In other words, the high viscosity necessary for casting militates against the preparation of dosage forms, which rapidly dissolve and disperse in the mouth.

We have now found that by an appropriate choice of film-forming components, specifically pullulan and sodium alginate, it is possible to provide a composition having the viscosity necessary for casting which, by appropriate treatment after casting, gives a dosage form capable of providing a low viscosity solution when placed in the mouth of the consumer. Thus, for the first time, there is provided a process for preparing orally consumable dosage forms which have the handling properties necessary for manufacture <u>and</u> rapidly dissolve and disperse in the mouth.

The dosage forms obtained by the process of the invention may be used for the administration of pharmaceutically active agents to both humans and animals. Of the latter, companion animals, particularly cats, dogs and horses, are considered especially suitable for the administration of drugs in this way.

While primarily intended for the administration of drugs suitable for oral delivery, the dosage forms of the invention may be used for the administration of pharmaceutically active agent(s) to any suitable mucosal surface, for example, the eyes, as well as to wound surfaces.

For the purposes of the present invention, the term 'pharmaceutically active agent' is used to describe any drug which is suitable for the treatment of a human or an animal and includes oral healthcare actives such as deodorising agents, anti-microbial agents and salivary stimulants.

The term 'volatile acid' is used herein to describe an acid which is wholly or substantially wholly removed (>95%) under the drying conditions of the process (step (c)). It follows that the term 'non-volatile acid' is employed herein to describe an acid which does not meet this criterion.

The term 'casting' is used herein to describe the means by which the compositions of the invention are shaped into dosage forms. Typically, the composition of the invention is cast on a suitable substrate, typically a glass plate, but alternative means such as extrusion through a slit orifice onto a substrate or the use of a mould may be employed. The requirements of the invention regarding viscosity are the same regardless of the means by which the compositions are cast.

Viscosity (Pa.s) may be defined as the shear stress (Pa) of a solution or composition divided by the shear rate (s^{-1}) at which the shear stress is measured.

For the purposes of this invention, the terms 'high' and 'low' viscosity are defined in terms of the difference in shear stress between the composition used for casting and the solution formed in the mouth. The term 'low' is employed when the viscosity of the solution formed in the mouth is less than 80% that of the composition used for casting, both being measured at a shear rate of $100s^{-1}$ and, in respect of measurement of the casting composition, after the composition has been allowed to stand for 24 hours. [It is not a necessary feature of the invention that the casting composition be allowed to stand for this period, but it serves as a convenient point in time at which to measure viscosity.]

By way of example, the viscosities of compositions in accordance with the invention comprising *ca.*16.5 wt% pullulan and different amounts of sodium alginate at pH 3.5 and pH 7.0 are shown in the following table:

wt% sodium alginate	Viscosity		% reduction in viscosity
	At pH 3.5	At pH 7.0	
0.42	3.7	2.9	22
0.83	8.0	5.3	34

1.7	16.2	9.8	40

It may be seen that compositions having a pH of 7.0, that is, approximating to the pH of the mouth, have viscosities at least 20% less than those observed at pH 3.5, the preferred pH of the casting compositions of the invention.

According to the present invention, therefore, there is provided a process for preparing an orally consumable dosage form which affords a low viscosity solution when placed in the mouth of the consumer, which process comprises the steps of

(a) preparing a hydrated polymer composition comprising pullulan and sodium alginate having a viscosity suitable for casting;

(b) casting said composition into the shape of a dosage form; and

(c) drying said dosage form under such conditions as to provide a dosage form which rapidly dissolves and disperses in the mouth of the consumer.

By adjusting the pH using a volatile acid, such as hydrochloric acid, it is possible to obtain a pullulan/sodium alginate composition of suitable viscosity for casting. By volatilising said acid after casting, a dosage form is produced which affords a low viscosity solution when placed in the mouth of the consumer. Other volatile acids suitable for the purposes of this embodiment include acetic acid and formic acid.

Thus according to a preferred first embodiment of the invention, there is provided a process which comprises the steps of

(a) preparing a hydrated polymer composition comprising pullulan, sodium alginate and one or more pharmaceutically active agents, which composition has a pH in the range 3.5 to 4.0, preferably about 3.5, said pH being achieved by the addition of a suitable volatile acid;

(b) casting said composition into the shape of a dosage form; and

(c) drying said dosage form under such conditions as to volatilise the acid and provide a dosage form which rapidly dissolves and disperses in the mouth of the consumer.

By adjusting the pH using a non-volatile acid, such as citric acid, it is possible, as with a volatile acid, to obtain a pullulan/sodium alginate composition of suitable viscosity for casting. When the resulting dosage form is placed in the mouth of the consumer, the increase in pH produced by the buffering effect of the saliva, typically to a value of 4.0 or greater, affords a low viscosity solution in accordance with the invention. Other non-volatile acids suitable for the purposes of this embodiment include aspartame, aspartic acid, benzoic acid, gluconic acid, glutamic acid, malic acid, phosphoric acid, saccharin, sorbic acid, succinic acid and tartaric acid. Some of these acids may also act as saliva-stimulating agents (see later).

Thus according to a second preferred embodiment, there is provided a process which comprises the steps of

(a) preparing a hydrated polymer composition comprising pullulan, sodium alginate and one or more pharmaceutically active agents, which composition has a pH in the range 3.5 to 4.0, preferably about 3.5, said pH being achieved by the addition of a suitable non-volatile acid;

(b) casting said composition into the shape of a dosage form; and

(c) drying said dosage form to provide a dosage form which rapidly dissolves and disperses in the mouth of the consumer when exposed to the buffering effect of saliva.

In the manufacture of soft centre chocolates, a thick paste containing an enzyme is used to form the centre of the confection. In the period between manufacture and consumption, the enzyme degrades the substance of the paste to give a liquid centre. Such technology may be used to provide a dosage form, which affords a low viscosity solution when placed in the mouth of the consumer.

Thus according to a third preferred embodiment of the invention, there is provided a process which comprises the steps of

(a) preparing a hydrated polymer composition comprising pullulan, sodium alginate and one or more pharmaceutically active agents, which composition additionally comprises one or both of the enzymes pullulanase and alginate lyase;

(b) casting said composition while still viscous into the shape of a dosage form; and

(c) drying said dosage form to provide a form which rapidly dissolves and disperses in the mouth of the consumer.

Some materials are known to be unstable to radiation. Sodium alginate formulations, for example, reduce in viscosity when exposed to gamma-radiation. Thus a viscous mixture of pullulan and sodium alginate may be used for casting and the viscosity of the alginate component subsequently reduced by gamma-irradiation, typically 25 kGy or 40kGy, to give a dosage form which affords a low viscosity solution when placed in the mouth of the consumer.

Thus according to a fourth preferred embodiment, there is provided a process which comprises the steps of

(a) preparing a hydrated polymer composition comprising pullulan, sodium alginate and one or more pharmaceutically active agents;

(b) casting said composition into the shape of a dosage form;

(c) drying said dosage form; and

(d) irradiating said dosage form with gamma-radiation to provide a form which rapidly dissolves and disperses in the mouth of the consumer.

Also within the scope of the present invention are dosage forms, particularly orally consumable films, prepared by the process of the invention. The dosage forms of the invention dissolve in the mouth to form a low viscosity solution, which rapidly disperses the pharmaceutically active agent(s) contained therein.

Protection is especially sought for orally consumable dosage forms according to the invention, which contain ibuprofen, ivermectin, or any form of eletriptan (including the free base, salts and polymorphs thereof).

Dosage forms, particularly orally consumable films, wherein the pharmaceutically active agent is the anti-migraine drug eletriptan hydrobromide (Relpax™) or eletriptan hemisulphate are especially preferred.

As indicated, the process of the invention requires that the composition used for manufacture of the dosage form have a higher viscosity than the solution produced in the mouth of the consumer.

In addition to those means already described as preferred embodiments of the invention, *viz.* adjusting the pH using a volatile acid or involatile acid, enzymatic degradation and irradiation, other means of adjusting the viscosity of the composition are available to a skilled person. These include (1) cooling or heating, (2) the addition/removal of electrolytes, (3) use of a shear-thickening polymer/surfactant and (4) use of particulates:

(1) Cooling or heating

Some materials exhibit rheological properties, which are temperature-dependent.

For example, carrageenan (at low pH) and agar have structures, which are readily disrupted by an increase in temperature. A high viscosity, low temperature composition could be used for casting and heat applied during subsequent drying to disrupt the structure. The significantly reduced molecular mobility in the dried film would inhibit the rate of reformation of the

structure. By judicious choice of heating and drying rates, it should be possible to balance the rate of viscosity loss on heating with the rate of viscosity increase on drying in order to trap the low viscosity form. When placed in the mouth, the lifetime of the product will be relatively short and dissolution and dispersion should occur before equilibrium thickening.

In contrast to carrageenan, some polymers, such as methyl cellulose, reversibly gel, *i.e.* increase in viscosity, when heated. A high temperature, high viscosity composition could be used for casting and then cooled during subsequent drying to provide a dosage form which would afford a low viscosity solution in the mouth of the consumer.

(2) Addition/removal of electrolytes

Electrolytes can also be used to modify the rheological properties of materials. For example, adding calcium ions to alginates and pectins can lead to thickening and gelation. Similarly, the properties of carboxymethyl cellulose and chitosan can be modified by the presence or absence of electrolytes. The binding of ionic species by, for example, chelation, during the period between casting and use would provide a dosage form which, when placed in the mouth, would afford a solution having a lower viscosity than that of the composition used for casting. It is envisaged that such viscosity-modifying electrolytes or electrolyte-binding species would be contained in a second film bound, after initial drying, to the film comprising the pharmaceutically active agent.

(3) Use of shear-thickening polymer/surfactant

By stirring in the presence of a shear-thickening polymer and/or surfactant, it is possible to provide a composition having the viscosity necessary for casting. The resulting dosage form will, in due course, revert to its original viscosity. An example of a shear-thickening surfactant is cetyltrimethylammonium tosylate (CTAT).

(4) Use of particulates

The addition of relatively high concentrations of particulates (especially irregularly-shaped particulates) can also increase viscosity. The particulates should be sufficiently fine not to feel 'gritty' in the mouth, typically <50μM. By adding a sufficient amount of particulates (such as silica or titanium dioxide particles), it is possible to provide a composition having the viscosity necessary for casting. When the resulting dosage form is placed in the mouth, the particulates therein will hinder polymer-polymer contact so that the polymers quickly redisperse.

The dosage forms of the invention typically comprise the film-forming agents pullulan and sodium alginate, one or more pharmaceutically active agents and at least one of the following additional agents: plasticising agent, saliva-stimulating agent, cooling agent, surfactant, emulsifying agent, sweetener, flavouring and/or fragrance, colouring agent, preservative, a triglyceride, a polyethylene oxide and propylene glycol.

Pullulan is a bioadhesive polysaccharide commonly employed in the preparation of orally consumable dosage forms and is used in the dosage forms of the invention in an amount of up to 70 wt%, preferably from 5 to 45 wt%, more preferably from 15 to 25 wt% and most preferably about 20 wt%.

Sodium alginate is a naturally-occurring copolymer of mannuronic and guluronic acid salts. It is water-soluble above pH 4.0, but under more acidic conditions is converted to the insoluble, but water-swellable, alginic acid. It is used in the dosage forms of the invention in an amount of up to 5.0 wt%, preferably from 0.1 to 2.5 wt% and most preferably about 0.5 wt%.

Pharmaceutically active agents, which may be delivered using dosage forms prepared by the process of the invention include

analgesic anti-pyretics;
anti-diarrhoeals;

anti-histamines;
anti-microbials;
anti-Parkinsonism drugs;
anti-tussives/cough suppressants;
bronchodilators;
decongestants;
drugs which selectively modify CNS function;
drugs for treating gastric disorders;
expectorants;
general non-selective CNS depressants;
general non-selective CNS stimulants;
H_2-antagonists;
narcotic analgesics;
non-steroidal anti-inflammatory drugs;
oral insulin;
proton pump inhibitors;
psychopharmacological drugs; and
wound-healing drugs

Specific examples of the foregoing drugs are to be found in the aforementioned WO 01/70194.

Other actives that may be delivered using dosage forms prepared by the process of the invention include

Anti-cholesterolaemics, for example, Lipitor™;
anti-emetics, for example, ondansetron;
anti-fungals, for example, fosfluconazole;
anti-infectives other than anti-microbial agents, for example, azithromycin;
anti-inflammatories, for example, Rimidil™;
anti-parasitic agents, for example, Pyrantel™;
anti-pyretics other than analgesic anti-pyretics;
appetite stimulants, for example, megatrol acetate;
cardiovascular drugs (including anti-hypertensives), for example, Norvasc™;

drugs for renal failure, for example, frusemide; and
PDE5 inhibitors, for example, Viagra™.

The dosage forms of the invention may contain one or more pharmaceutically active agents, which agents may or may not be of the same therapeutic type. Thus a dosage form according to the invention could contain an anti-tussive plus an anti-histamine, a nasal decongestant or bronchodilator, an analgesic, an anti-inflammatory, a cough suppressant and/or an expectorant.

The amount of pharmaceutically active agent provided in each dosage form will obviously be dependent on the dose needed to provide an effective amount. Furthermore, the amount provided may be adjusted to deliver a predetermined dose over a predetermined period of time. The concentration of active agent(s) for pharmaceutical and veterinary products in accordance with the invention may be up to 75% w/w, but is typically in the range 0.1 to 50% w/w. Typical doses which can be delivered per dosage form are in the range 10μg to 100mg.

The dosage forms of the invention may also be used to deliver oral healthcare products, such a deodorising agents, anti-microbial agents and salivary stimulants. The concentration of active agent(s) for oral healthcare products is typically in the range 0.1 to 15% w/w. Typical doses which can be delivered per dosage form are comparable to those for pharmaceutical and veterinary products, *viz.* from 10μg to 100mg.

Preferred pharmaceutically active agents for delivery by means of the dosage forms of the invention include ibuprofen, ivermectin and any form of eletriptan (including the free base, salts and polymorphs thereof).

The anti-migraine drugs eletriptan hydrobromide (Relpax™) and eletriptan hemisulphate are especially preferred for delivery by this means. Thus a dosage form, typically an orally consumable film, prepared according to the process of the invention may be used to deliver an effective amount of Relpax™ to a migraine sufferer in need of such treatment. For a film prepared by the process of the invention

measuring 2.2cm x 3.2cm and weighing from 60 to 190mg, the typical adult dose of Relpax™would be in the range 5 to 80mg.

Preferred plasticising agents include monoacetin, diacetin and triacetin, polyalcohols, such as glycerol and glycerol monoesters, and sorbitol, which may be present in the dosage forms of the invention in an amount of from 0 to 20 wt%, preferably from 0 to 2 wt%.

Preferred saliva-stimulating agents include citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids which may be present in the

dosage forms of the invention in an amount of from 0.01 to 12 wt%, preferably from 1 to 10 wt% and most preferably from 2.5 to 6 wt%.

Preferred cooling agents include monomenthyl succinate, WS3, WS23 and Ultracool II which may be present in the dosage forms of the invention in an amount of from 0.001 to 2.0 wt%, preferably from 0.2 to 0.4 wt%.

Preferred surfactants include mono- and diglycerides of fatty acids, polyoxyethylene sorbitol esters and di- and tri-block copolymers, such as pluronics, which may be present in the dosage forms of the invention in an amount of from 0.5 to 15 wt%, preferably 1 to 5 wt%.

Preferred emulsifying agents include triethanolamine stearate and quaternary ammonium compounds which may be present in the dosage forms of the invention in an amount of from 0 to 5 wt%, preferably from 0.01 to 0.7 wt%.

Suitable sweeteners, both natural and artificial, may be used in the dosage forms of the invention in an amount effective to provide the desired level of sweetness. This amount will typically be in the range 0.01 to 10 wt%, preferably from 2 to 5 wt%.

Suitable flavourings and/or fragrances include those well known in the art, both natural and artificial, which may be used in the dosage forms of the invention in an amount sufficient to give the desired flavour/fragrance. This amount will typically be in

the range 0.1 to 30 wt%, preferably from 2 to 25 wt%, most preferably from 8 to 10 wt%.

Suitable colouring agents include those well known in the art, for example, titanium oxide, which may be used in the dosage forms of the invention in an amount sufficient to give the desired colouring. This amount will typically be in the range up to about 5 wt%, preferably less than 1 wt%.

Preferred preservatives include sodium benzoate and potassium sorbate which may be present in the dosage forms of the invention in an amount of from 0.001 to 5 wt%, preferably from 0.01 to 1 wt%.

The dosage forms of the invention may also include a triglyceride, such as olive oil, which may be present in an amount of from 0.1 to 12 wt%, preferably from 0.5 to 9 wt%. They may also contain a polyethylene oxide such as N-10 (Union Carbide) having a molecular weight of from 50,000 to 6,000,000, which may be present in an amount of from 0.1 to 5 wt%, preferably from 0.2 to 4.0 wt%.

The dosage forms of the invention may also contain propylene glycol in an amount of from 1 to 20 wt%, preferably from 5 to 15 wt%.

Finally, it may be desirable to taste-mask the dosage forms of the invention using means well known to those skilled in the art, for example, as described

in A Nanda *et al*, Indian Journal of Pharmaceutical Sciences, 64(1), 10-17 (2002) and the aforementioned WO 01/70194.

According to the first preferred embodiment, step (a), preparation of the pH-adjusted hydrated polymer composition for casting, is typically carried out by

(i) mixing the film-forming ingredients in water and allowing to hydrate;

(ii) dissolving the water-soluble ingredients in water and adding the aqueous solution to the composition resulting from step (i);

(iia) adjusting the pH of the composition to a pH in the range 3.5 to 4.0, preferably about pH 3.5, using a suitable volatile acid; and

(iii) mixing in the organic ingredients and surfactants.

According to the second preferred embodiment, step (a), preparation of the pH-adjusted hydrated polymer composition for casting, is typically carried out by

(i) mixing the film-forming ingredients in water and allowing to hydrate;

(ii) dissolving the water-soluble ingredients in water and adding the aqueous solution to the composition resulting from step (i);

(iia) adjusting the pH of the composition to a pH in the range 3.5 to 4.0, preferably about 3.5, using a suitable non-volatile acid; and

(iii) mixing in the organic ingredients and surfactants.

According to the third preferred embodiment, step (a), preparation of the hydrated polymer composition for casting, is typically carried out by

(i) mixing the film-forming ingredients in water and allowing to hydrate;

(ii) dissolving the water-soluble ingredients, including the pullulanase and alginate lyase, in water and adding the aqueous solution to the composition resulting from step (i);

(iii) mixing in the organic ingredients and surfactants.

Alternatively, the pullulanase and alginate lyase may be added, not in step (ii), but in a separate step (iv).

According to the fourth preferred embodiment, step (a), preparation of the hydrated polymer composition for casting, is typically carried out by

(i) mixing the film-forming ingredients in water and allowing to hydrate;

(ii) dissolving the water-soluble ingredients in water and adding the aqueous solution to the composition resulting from step (i);

(iii) mixing in the organic ingredients and surfactants.

For the purposes of step (i), the film-forming ingredients, typically comprising pullulan and sodium alginate, are mixed in water, preferably deionised and at a temperature of from 10°C to 90°C, and allowed to hydrate for from 30 minutes to 48 hours to form a gel. The resulting gel contains from 40 to 80 wt% of water and is cooled to 20-30°C over a period of from 1 to 48 hours.

For the purposes of step (ii), the water-soluble ingredients, typically comprising the pharmaceutically active agent, colouring agent, preservative and sweetener, are dissolved in deionised water at a temperature of from 25°C to 45°C. The amount of water used is typically from 5 to 80 wt% of the final composition.

It is also within the scope of the invention that a pharmaceutically active agent, which is of limited solubility in water may be used in step (ii) as a suspension thereof.

Steps (i) and (ii) may be transposed, that is, the water-soluble ingredients may be dissolved in water to which the film-forming ingredients are added.

For the purposes of step (iia) of the first and second embodiments, the pH of the composition is adjusted to a pH in the range 3.5 to 4.0, preferably about 3.5, using a volatile or involatile acid as hereinbefore defined.

For the purposes of step (iii), the organic ingredients and surfactants are typically added in undiluted form to the composition resulting from the preceding step.

Steps (iia) and (iii) in the first and second embodiments may be transposed, that is, pH adjustment may be carried out <u>after</u> addition of the organic ingredients and surfactants.

The mixture resulting from steps (i) to (iii) is then emulsified by vigorous stirring and, for the purpose of making a dosage form in accordance with the invention, cast, typically within 24 hours of gel preparation, on a suitable substrate, typically a glass plate, preferably covered with an appropriate backing paper.

The resulting film is then dried, typically within 24 hours of casting, in a fan oven at a temperature of from 50°C to 80°C, preferably about 60°C, for from 15 to 90 minutes, or in a coating machine, such as a Labcoater Type LTE-S manufactured by Werner Mathis AG Oberhasli Switzerland or similar, at a

temperature of from 20°C to 150°C, cut to the desired dimensions, packaged and stored. The final film ideally contains from 0.1 to 10 wt% moisture, preferably from 3 to 8 wt% and most preferably from 4 to 7 wt%.

The invention is illustrated by reference to the following Examples, which are not intended to be limiting in any way.

EXAMPLE 1

A 16.5 wt% pullulan/0.83 wt% sodium alginate composition was prepared as follows:

Pullulan (20.0g) and sodium alginate (1.0g) were added to deionised water (100mL) and the mixture left to equilibrate overnight. The pH of the resulting gel was adjusted to 3.5 using dilute hydrochloric acid. To 31.7g of the gel was added ibuprofen (3.5g) and the mixture stirred vigorously.

A film in accordance with the invention was prepared by applying the gel to a glass plate, coated with an appropriate backing paper, using a CAMAG hand-operated coater having a 0.5mm gate. The resulting film was dried in a fan oven at 80°C for 30 minutes.

When dry, the film provided an ibuprofen concentration of 36.6% w/w, that is, about 32mg of ibuprofen in a film 2.2cm x 3.2cm.

To 25.8g of unused gel were added glycerol (0.28g) and a second film prepared in the same way. When dry, the film provided an ibuprofen concentration of 35.0% w/w, that is, again about 32mg of ibuprofen in a film 2.2cm x 3.2cm. The resulting film was less brittle, *i.e.* less prone to cracking, than that prepared without glycerol.

When placed in the mouth, the rehydrated films both gave low viscosity solutions, which rapidly dissolved and dispersed.

EXAMPLE 2

A 17.1 wt% pullulan/0.85 wt% sodium alginate composition comprising glycerol and potassium sorbate was prepared as follows:

Pullulan (20.0g), sodium alginate (1.0g), glycerol (1.25g) and potassium sorbate (0.07g) were added to deionised water (95mL) and the mixture left to equilibrate overnight. The pH of the resulting gel was adjusted to 3.5 using dilute hydrochloric acid. To 31.7g of the gel was added ibuprofen (3.17g) and the mixture stirred vigorously.

A film in accordance with the invention was prepared by applying the gel to a glass plate, coated with an appropriate backing paper, using a CAMAG hand-

operated coater having a 0.5mm gate. The resulting film was dried in a fan oven at 80°C for 30 minutes.

When dry, the film provided an ibuprofen concentration of 34.5% w/w, that is, about 32mg of ibuprofen in a film 2.2cm x 3.2cm.

When placed in the mouth, the re-hydrated film gave a low viscosity solution, which rapidly dissolved and dispersed.

EXAMPLE 3

A 20.0 wt% pullulan/1.0 wt% sodium alginate composition was prepared as follows:

Pullulan (20.0g) and sodium alginate (1.0g) were added to deionised water (79mL) and the mixture left to stand overnight. The pH of the resulting gel was adjusted to 3.5 using dilute hydrochloric acid. To 35g of the gel was added eucalyptol (0.06g), *l*-menthol (0.6g), methyl salicylate (0.04g), thymol (0.04g) and mint oil (0.8g) and the mixture stirred vigorously.

A film in accordance with the invention was prepared by applying the gel to a glass plate, coated with an appropriate backing paper, using a CAMAG hand-operated coater having a 0.25mm gate. The resulting film was dried in a fan oven at 80°C for 30 minutes.

When dry, the film provided concentrations and weights/film of eucalyptol (0.06g), *l*-menthol (0.60g), methyl salicylate (0.04g), thymol (0.04g) and mint oil (0.80g) of

Ingredient	Concentration (% w/w)	Weight/film (mg)
Eucalyptol	0.67	0.29
l-Menthol	6.75	2.89
Methyl salicylate	0.45	0.19
Thymol	0.45	0.19
Mint oil	9.0	3.85

in a film 2.2cm x 3.2cm.

When placed in the mouth, the rehydrated film gave a low viscosity solution which rapidly dissolved and dispersed.

EXAMPLE 4

A 16.2 wt% pullulan/0.81 wt% sodium alginate composition comprising glycerol and potassium sorbate was prepared as follows:

Pullulan (20.0g), sodium alginate (1.0g), glycerol (2.5g) and potassium sorbate (0.14g) were added to deionised water (100mL) and the mixture left to equilibrate overnight. The pH of the resulting gel was adjusted to 3.5 using dilute hydrochloric acid. To 15mL of the gel was added a solution of ivermectin (3.4mg) in methanol (0.75mL) and the mixture stirred vigorously.

A film in accordance with the invention was prepared by applying the gel to a glass plate, coated with an appropriate backing paper, using a CAMAG hand-operated coater having a 0.5mm gate. The resulting film was dried in a fan oven at 80°C for 16 minutes.

When dry, the film provided an ivermectin concentration of 0.12% w/w, that is, about 76μg of ivermectin in a film 2.2cm x 3.2cm.

When placed in the mouth of a dog, the rehydrated film gave a low viscosity solution, which rapidly dissolved and dispersed.

EXAMPLE 5

A 16.6 wt% pullulan/0.42 wt% sodium alginate composition was prepared as follows:

Pullulan (20.0g) and sodium alginate (0.5g) were added to deionised water (100mL) and the mixture left to equilibrate overnight. The pH of the resulting gel was adjusted to pH 3.5 using a dilute solution of citric acid (0.1M) and the mixture stirred vigorously. During this procedure, a pharmaceutically active agent may be added to the mixture.

A film in accordance with the invention was prepared by applying the gel to a glass plate, coated with an appropriate backing paper, using a CAMAG hand-operated coater having a 0.5mm gate The resulting film was dried in a fan oven at 65°C for 20 minutes.

When placed in the mouth, the rehydrated film gave a low viscosity solution, which rapidly dissolved and dispersed.

EXAMPLE 6

A 16.4 wt% pullulan/1.64 wt% sodium alginate composition was prepared as follows:

Pullulan (20.0g) and sodium alginate (2.0g) were added to deionised water (100mL) and the mixture left to equilibrate overnight. Pullulanase (125µL, 400 units/mL) and alginate lyase (0.5mg) were added to the resulting gel and the mixture stirred vigorously. During this procedure, a pharmaceutically active agent may be added to the mixture.

The gel remained sufficiently viscous for the purposes of casting for a period of 10-15 minutes, though by judicious selection of enzyme concentrations this period could be extended from, say, 60 minutes to several hours should the casting time require it.

A film in accordance with the invention was prepared by applying the gel to a glass plate, coated with an appropriate backing paper, using a CAMAG hand-operated coater having a 0.5mm gate. The resulting film was dried in a fan oven at 65°C for 25 minutes.

When placed in the mouth, the rehydrated film gave a low viscosity solution, which rapidly dissolved and dispersed.

EXAMPLE 7

A 16.4 wt% pullulan/1.64 wt% sodium alginate composition was prepared as follows:

Pullulan (20.0g) and sodium alginate (2.0g) were added to deionised water (100mL) and the mixture left to equilibrate overnight. During this procedure, a pharmaceutically active agent may be added to the mixture.

A film in accordance with the invention was prepared by applying the gel to a glass plate, coated with an appropriate backing paper, using a CAMAG hand-operated

coater having a 0.5mm gate. The resulting film was dried in a fan oven at 65ºC for 25 minutes and then gamma-irradiated at 25 kGy or 40 kGy.

When placed in the mouth, the rehydrated film gave a low viscosity solution, which rapidly dissolved and dispersed.